**Final Report for Period:** 07/2010 - 12/2010
**Submitted on:** 03/30/2011
**Principal Investigator:** Sherrill, Charles D.
**Award ID:** 0715268
**Organization:** GA Tech Res Corp - GIT
**Submitted By:**
Sherrill, Charles - Principal Investigator
**Title:**
Theoretical Models for Potential Energy Landscapes of Challenging Chemical Systems

## Project Participants

**Senior Personnel**

**Name:** Sherrill, Charles
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**

**Post-doc**

**Name:** Burns, Lori
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**

**Graduate Student**

**Name:** Ringer, Ashley
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**
Ashley is an NSF Graduate fellow who has been working on the project

**Name:** March, William
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**

**Name:** Riegel, Ryan
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**

**Name:** Hohenstien, Edward
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**

**Name:** Kennedy, Matthew
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**

**Name:** Marshall, Michael
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**

**Undergraduate Student**

**Name:** McClean, Jarrod

**Worked for more than 160 Hours:** Yes

**Contribution to Project:**

Undergraduate student from Berkeley developed and implemented a new polarizable force field parameterized against our very-high-quality quantum benchmarks for noncovalent interactions.

**Name:** Breuer, Marian

**Worked for more than 160 Hours:** Yes

**Contribution to Project:**

International REU student from Jacobs University, Germany, tested new damping functions for the DFT-D method

**Name:** Geng, Yue

**Worked for more than 160 Hours:** No

**Contribution to Project:**

Georgia Tech student Yue Geng worked on the project, supported by a Georgia Tech Presidential Undergraduate Research Award. She is first author of a paper on indole-benzene.

**Technician, Programmer**

**Other Participant**

**Research Experience for Undergraduates**

**Name:** Chill, Samuel

**Worked for more than 160 Hours:** Yes

**Contribution to Project:**

REU student Sam Chill tested M05-2X versus DFT-D and found the latter more effective for interstrand base-pair noncovalent interactions.

**Years of schooling completed:** Junior

**Home Institution:** Other than Research Site

**Home Institution if Other:** University of Tennessee, Chattanooga

**Home Institution Highest Degree Granted(in fields supported by NSF):** Master's Degree

**Fiscal year(s) REU Participant supported:** 2008

**REU Funding:** REU supplement

## Organizational Partners

**Q-Chem, Inc.**

We added empirical dispersion corrections for Hartree-Fock/DFT to both the PSI and Q-Chem packages to increase the availability of this promising method.

## Other Collaborators or Contacts

We have worked closely with Prof. Alex Gray (Georgia Tech College of Computing) and members of his research group to explore very ambitious work at the interface of theoretical chemistry and computational chemistry, in particular, fast algorithms for three-body dispersion in molecular dynamics simulations, and improvements to fast-multipole approaches to Hartree-Fock (described in more detail in the report).

We have worked closely with the groups of Profs. Daniel Crawford and Edward Valeev (Virginia Tech) to improve and expand the open-source electronic structure program PSI3.

We have collaborated with Prof. Anna Krylov (USC) in a careful theoretical examination of radical cation dimers, where we used our group's full configuration interaction program to benchmark the reliability of equation-of-motion coupled-cluster techniques for these challenging

systems.

In collaboration with the Schaefer group at UGA, we have implemented a more efficient version of our MP2-CCSD hybrid theory, which aims to achieve good CCSD quality at a lower MP2-type cost. Additional tests of this approach are being run using the new code.

Using our DFT-D code, we assisted Georgia Tech Professor Facundo Fernandez in interpreting experimental results for the rapid screening of the drug tamiflu, which will help in efforts to arrest drug counterfeiting in the third world.

In collaboration with Kenneth Merz, we examined the interaction of indinavir with HIV-II protease.

## Activities and Findings

**Research and Education Activities: (See PDF version submitted by PI at the end of the report)**

**Findings: (See PDF version submitted by PI at the end of the report)**

**Training and Development:**

Project personnel have an opportunity to learn a healthy mix of electronic structure theory and applied computational chemistry in the Sherrill group. Much of our development work is inspired by chemical applications we pursue, and conversely we are often able to tackle applied projects more effectively because of the development and testing of new methods.

The PI has established an annual Summer Theory Program at Georgia Tech for undergraduate researchers and beginning graduate students. The program involves introductory lectures in theoretical chemistry in addition to summer research. Approximately eleven NSF REU students at Georgia Tech have gone through the program to date. All REU students and beginning graduate students write their own Hartree-Fock programs as part of an educational program that includes theoretical methods as well as applications of quantum chemistry.

Several of our projects go beyond traditional small-molecule quantum chemistry and have included Protein Data Bank (PDB) data mining, solid-state calculations, molecular dynamics simulations, etc. We also have a good number of collaborations with other theorists and experimentalists, exposing students to a wide array of techniques and challenges.

**Outreach Activities:**

The PI has been very active in outreach activities throughout his career. These have included appearing on the public radio program ``Science in Your Life," advising the Food TV program ``Good Eats," teaching the NSF Workshop in Theoretical and Computational Chemistry, instituting the Summer Lecture Series in Theoretical Chemistry at Georgia Tech, and serving as Chair of the Georgia Section of the American Chemical Society (ACS). The Georgia Section of the ACS won four national ChemLuminary awards for 2006, the year in which Dr. Sherrill served as chair. Several of these awards were for public outreach efforts, including Best New Public Relations Program of a Local Section.

Dr. Sherrill was a councilor of the Georgia Section and also served as a member of the executive committee of the PHYS division of the ACS (2007-2010). He has also proceeded through the officer succession of the Theoretical Chemistry subdivision of the ACS and is currently Chair. In these positions, he is continuing his efforts to advocate for public awareness and education in chemistry. Dr. Sherrill also continues to develop an award-winning set of educational notes on quantum chemistry available at his website; these are accessed by graduate, undergraduate, and even high-school students. These notes are in the top-10 hits on a Google search of ``Quantum Chemistry."

## Journal Publications

Temelso, B; Sherrill, CD; Merkle, RC; Freitas, RA, "Ab initio thermochemistry of the hydrogenation of hydrocarbon radicals using silicon-, germanium-, tin-, and lead-substituted methane and isobutane", JOURNAL OF PHYSICAL CHEMISTRY A, p. 8677, vol. 111, (2007). Published, 10.1021/jp071797

Ringer, AL; Senenko, A; Sherrill, CD, "Models of S/pi interactions in protein structures: Comparison of the H2S-benzene complex with PDB data", PROTEIN SCIENCE, p. 2216, vol. 16, (2007). Published, 10.1110/ps.07300230

Pieniazek, PA; Arnstein, SA; Bradforth, SE; Krylova, AI; Sherrill, CD, "Benchmark full configuration interaction and equation-of-motion coupled-cluster model with single and double substitutions for ionized systems results for prototypical charge transfer systems: Noncovalent ionized dimers", JOURNAL OF CHEMICAL PHYSICS, p. , vol. 127, (2007). Published, 10.1063/1.279570

T. Takatani and C. D. Sherrill, "Performance of Spin-component-scaled Moller-Plesset Theory (SCS-MP2) for Potential Energy Curves of Noncovalent Interactions", Phys. Chem. Chem. Phys., p. 6106, vol. 9, (2007). Published, 10.1039/b709669k

A. L. Ringer, C. D.Sherrill, R. A. King, and T. D. Crawford, "Low-Lying Singlet Excited States of Isocyanogen", Int. J. Quantum Chem., p. 1137, vol. 108, (2008). Published, 10.1002/qua

A. L. Ringer and C. D. Sherrill, "First Principles Computation of Lattice Energies of Organic Solids: The Benzene Crystal", Chem. Eur. J., p. 2542, vol. 14, (2008). Published, 10.1002/chem.200701622

Hohenstein, EG; Chill, ST; Sherrill, CD, "Assessment of the Performance of the M05-2X and M06-2X Exchange-Correlation Functionals for Noncovalent Interactions in Biomolecules", JOURNAL OF CHEMICAL THEORY AND COMPUTATION, p. 1996, vol. 4, (2008). Published, 10.1021/ct800308

Arnstein, SA; Sherrill, CD, "Substituent effects in parallel-displaced pi-pi interactions", PHYSICAL CHEMISTRY CHEMICAL PHYSICS, p. 2646, vol. 10, (2008). Published, 10.1039/b718742

Takatani, T; Hohenstein, EG; Sherrill, CD, "Improvement of the coupled-cluster singles and doubles method via scaling same- and opposite-spin components of the double excitation correlation energy", JOURNAL OF CHEMICAL PHYSICS, p. , vol. 128, (2008). Published, 10.1063/1.288397

Nyadong, L; Hohenstein, EG; Johnson, K; Sherrill, CD; Green, MD; Fernandez, FM, "Desorption electrospray ionization reactions between host crown ethers and the influenza neuraminidase inhibitor oseltamivir for the rapid screening of Tamiflu (R)", ANALYST, p. 1513, vol. 133, (2008). Published, 10.1039/b809471

Marshall, MS; Steele, RP; Thanthiriwatte, KS; Sherrill, CD, "Potential Energy Curves for Cation-pi Interactions: Off-Axis Configurations Are Also Attractive", JOURNAL OF PHYSICAL CHEMISTRY A, p. 13628, vol. 113, (2009). Published, 10.1021/jp906086

Sherrill, CD; Sumpter, BG; Sinnokrot, MO; Marshall, MS; Hohenstein, EG; Walker, RC; Gould, IR, "Assessment of Standard Force Field Models Against High-Quality Ab Initio Potential Curves for Prototypes of pi-pi, CH/pi, and SH/pi Interactions", JOURNAL OF COMPUTATIONAL CHEMISTRY, p. 2187, vol. 30, (2009). Published, 10.1002/jcc.2122

Sherrill, CD; Takatani, T; Hohenstein, EG, "An Assessment of Theoretical Methods for Nonbonded Interactions: Comparison to Complete Basis Set Limit Coupled-Cluster Potential Energy Curves for the Benzene Dimer, the Methane Dimer, Benzene-Methane, and Benzene-H2S", JOURNAL OF PHYSICAL CHEMISTRY A, p. 10146, vol. 113, (2009). Published, 10.1021/jp903437

Johnson, ER; Becke, AD; Sherrill, CD; DiLabio, GA, "Oscillations in meta-generalized-gradient approximation potential energy surfaces for dispersion-bound complexes", JOURNAL OF CHEMICAL PHYSICS, p. , vol. 131, (2009). Published, 10.1063/1.317706

Ringer, AL; Sherrill, CD, "Substituent Effects in Sandwich Configurations of Multiply Substituted Benzene Dimers Are Not Solely Governed By Electrostatic Control", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, p. 4574, vol. 131, (2009). Published, 10.1021/ja809720

Hohenstein, EG; Sherrill, CD, "Effects of Heteroatoms on Aromatic pi-pi Interactions: Benzene-Pyridine and Pyridine Dimer", JOURNAL OF PHYSICAL CHEMISTRY A, p. 878, vol. 113, (2009). Published, 10.1021/jp809062

Hohenstein, EG; Sherrill, CD, "Density fitting of intramonomer correlation effects in symmetry-adapted perturbation theory", JOURNAL OF CHEMICAL PHYSICS, p. , vol. 133, (2010). Published, 10.1063/1.345107

Hohenstein, EG; Sherrill, CD, "Density fitting and Cholesky decomposition approximations in symmetry-adapted perturbation theory: Implementation and application to probe the nature of pi-pi interactions in linear acenes", JOURNAL OF CHEMICAL PHYSICS, p. , vol. 132, (2010). Published, 10.1063/1.342631

Geng, Y; Takatani, T; Hohenstein, EG; Sherrill, CD, "Accurately Characterizing the pi-pi Interaction Energies of Indole-Benzene Complexes", JOURNAL OF PHYSICAL CHEMISTRY A, p. 3576, vol. 114, (2010). Published, 10.1021/jp909949

Takatani, T; Hohenstein, EG; Malagoli, M; Marshall, MS; Sherrill, CD, "Basis set consistent revision of the S22 test set of noncovalent interaction energies", JOURNAL OF CHEMICAL PHYSICS, p. , vol. 132, (2010). Published, 10.1063/1.337802

Vazquez-Mayagoitia, A; Sherrill, CD; Apra, E; Sumpter, BG, "An Assessment of Density Functional Methods for Potential Energy Curves of Nonbonded Interactions: The XYG3 and B97-D Approximations", JOURNAL OF CHEMICAL THEORY AND COMPUTATION, p. 727, vol. 6, (2010). Published, 10.1021/ct900551

J. C. Faver, M. L. Benson, X. He, B. P. Roberts, B. Wang, M. S. Marshall, M. R. Kennedy, C. D. Sherrill, and K. M. Merz, "Formal Estimation of Errors in Computed Absolute Interaction Energies of Protein-Ligand Complexes", Journal of Chemical Theory and Computation, p. 790, vol. 7, (2011). Published, 10.1039/c0sc00517g

C. D. Sherrill, "Computations of Noncovalent Pi Interactions", Reviews in Computational Chemistry, p. 1, vol. 26, (2009). Published,

## Books or Other One-time Publications

C. D. Sherrill, A. Dutta, M. L. Abrams, and J. S. Sears, "Bond Breaking in Quantum Chemistry: A Comparison of Single- and Multi-Reference Methods", (2007). Book, Published
Editor(s): A. K. Wilson and K. A. Peterson
Bibliography: ACS Symposium Series, Vol. 958 (American Chemical Society, Washington, D.C.)

## Web/Internet Site

## Other Specific Products

## Contributions

**Contributions within Discipline:**

The Sherrill group continues to be one of the leaders in the benchmarking and calibration of new theoretical methods. This has a significant impact in helping computational chemists assess the reliability of various methods for a particular problem (the Reviews in Computational Chemistry chapter book chapter, the 2009 JPC A review article, and the full CI studies of van der Waals radical cations are just a few of our many published examples).

Our development of the new SCS-CCSD method, and the world's fastest wavefunction-based SAPT program, and our other contributions to the PSI3 program, provides new tools to computational chemists.

Our continued development of the PSI3 program, downloaded over 7000 times, also has a significant impact on theoretical and computational chemistry. The new PSI4 project will have an even larger impact because of the significant new features we are adding.

**Contributions to Other Disciplines:**

Our demonstration of a 'chemical accuracy' computation of the lattice energy of crystalline benzene will have significant effects on ab initio crystal structure prediction, which impacts not only theoretical chemistry but materials science.

Our finding that geometrical preferences of sulfur-pi interactions found in quantum computations of H2S-benzene align with statistical

information on sulfur-pi interactions in the protein data bank (PDB) have significant implications for biomolecular structure --- namely, that secondary interactions and solvent effects do not statistically wash out individual interaction preferences. This has profound implications about how to think about biomolecular structure, which in turn affects biochemistry, biology, and drug design.

**Contributions to Human Resource Development:**

Our web notes on quantum chemistry are a valued resource by curious graduate, undergraduate, and high-school students.

**Contributions to Resources for Research and Education:**

Our web notes on quantum chemistry are a valued resource by curious graduate, undergraduate, and high-school students.

**Contributions Beyond Science and Engineering:**

Our DFT-D computer code was used by graduate student Edward Hohenstein to assist the Fernandez group at Georgia Tech in developing a rapid screening method for the drug Tamiflu. This screening method will be used to detect counterfeit drugs which are particularly problematic in the third world.

## Conference Proceedings

Hohenstein, EG;Takatani, T;Sherrill, CD, PHYS 542-Improvement of CCSD correlation energies through scaling same-spin and opposite-spin components of the double excitations, "APR 06-10, 2008", ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, 235: - 542-PHYS APR 6 2008

Breuer, M;Sherrill, CD, CHED 278-Performance of DFT plus D for potential energy curves of noncovalent interactions, "AUG 17-21, 2008", ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, 236: - 278-CHED AUG 17 2008

Ringer, AL;Sherrill, CD, PHYS 489-First principles computation of lattice energies of organic solids: The benzene crystal, "AUG 17-21, 2008", ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, 236: - 489-PHYS AUG 17 2008

## Categories for which nothing is reported:

Any Web/Internet Site

Any Product

# Project Activities

## Goals

Our primary goal is to extend the reach of quantum chemistry methods to difficult cases. This project focuses on systems where electron correlation effects can be critical, either in those systems where more than one electron configuration is important (i.e., nondynamical electron correlation, such as bond-breaking reactions and diradicals), or in weakly-bound systems where qualitatively incorrect solutions are obtained unless robust models of dynamical correlation are employed.

We have pursued a dual-track strategy of (a) developing new theoretical methods and implementing them as efficient computer programs, and (b) applying new and existing methods to key prototype chemical systems which are challenging to model.

Our work has been presented at departmental seminars across the US and at numerous national and international conferences. It has also been disseminated through journal articles and book chapters.

## Activities

### Electronic structure programs

Much of our work involves theoretical development and computer programming. Believing that theoretical and computational chemistry research in the US will benefit tremendously from the widespread, free availability of tools for the development and application of electronic structure methods, we have embarked upon a project to make as many of these tools available as possible through our open-source program package, PSI3, developed in collaboration with the groups of Daniel Crawford and Edward Valeev (Virginia Tech). Our code is freely available at our website
`http://www.psicode.org`; to date, there have been over 7000 downloads of our software. The program has CI, MP2, CCSD, CCSD(T), CASSCF, MRCI, MP2-R12/A, and other capabilities. Version 3.4 of the software, reflecting numerous improvements, was released in February of 2009. We run yearly, multiple-day PSI3 programming workshops with other theory groups to extend the impact of this program. The most recent of these workshops within the reporting period was held in August 2010. In the past 3 years, we have made the following improvements to the PSI3 program:

- We have added spin-component-scaled (SCS) MP2 and CCSD capabilities (see below for more detail).

- The PI incorporated his prototype code for "macroconfiguration" coupled-cluster theory into PSI3 for testing by other PSI3 developers.
- The PI fully incorporated restricted-active-space self-consistent-field (RASSCF) energies and gradients, and complete-active-space SCF (CASSCF) gradients.
- In collaboration with our co-workers, we have made the program even easier to configure and install; this process now rivals or surpasses that of any alternative electronic structure programs.
- We have cleaned up some obsolete code in the CI module and the libraries.
- We have made massive improvements to the documentation for both users and developers.
- We have added a timings test suite so the performance of different computer hardware can be tested easily.
- We added empirical dispersion terms which can be added to Hartree-Fock (energies, gradients, and second derivatives). This code was also added to the Q-Chem program for Hartree-Fock or density functional theory.
- We added configuration interaction gradient capability.
- In collaboration with Prof. Rollin King (Bethel University), we have improved the geometry optimization module.
- We have added a density-fitted MP2 program.
- We have begun work on a density-fitted Hartree-Fock program.
- We implemented a very efficient density fitted symmetry-adapted perturbation theory (SAPT) program for low-order SAPT, and we began working on adding capabilities for higher-order SAPT.

Student Ashley Ringer wrote an interface between PSI3 and the popular WebMO program, to allow us to have a much greater impact with our software by reaching a much larger user base.

Students Edward Hohenstein and Michael Marshall took parallel programming classes to assist with parallelization efforts within PSI3. The entire group attended a one-week workshop on parallelization of quantum chemistry algorithms in August, 2009. This knowledge helped us in the redesign of the base libraries of PSI to enable future parallel programming development.

Toward the end of the grant period, we began laying the foundation for the next phase of our open-source quantum chemistry project. At the 2009 PSI Programmers' workshop, we kicked off development of PSI4, the next major release of the PSI package. This version will be developed to be an object-oriented, parallel code from the ground up (reusing bits of code from PSI3 where feasible). We are very excited about this new project and the renewal of this NSF project will allow us to continue this work.

## Theory development and benchmarking

As stated above, our project involves pushing quantum chemistry to treat challenging problems more reliably and/or efficiently. Over the past 3 years, we have focused particularly on improved methods for intermolecular interactions. We have investigated the very promising spin-component-scaled (SCS) MP2 method by Grimme, and we were the first to systematically compare this approach to benchmark-quality, large-basis CCSD(T) results for *potential energy curves*, not just minima [PCCP, 2007]. This paper also examined the reliability of local-correlation approximations for noncovalent interactions. In 2008, we were the first to introduce a higher-order SCS method, namely, SCS coupled-cluster singles and doubles (SCS-CCSD) [JCP]. We also began our own testing of the promising DFT-D approach, which adds empirical dispersion terms to DFT, as a possible solution for treating noncovalent interaction in very large molecules. In particular, we believe this method is more suitable than popular alternative DFT methods for situations where long-range dispersion is important, and we demonstrated (with 2008 summer REU student Samuel Chill) that it is superior to the M05-2X functional for interstrand base-pair interactions in DNA [JCTC, 2008]. International summer REU student Marian Breuer (Germany) tested different damping functions for the DFT-D method in the summer of 2008. In late 2009 and early 2010, we began a very serious systematic study of the performance of various DFT-D and double-hybrid approaches and damping functions. We published one paper on the XYG3 double-hybrid, and made major progress on a massive systematic benchmarking study on many different DFT-D/double-hybrid methods for non-bonded interactions [published subsequently in the renewal grant period in JCP, 2011]. As part of this work, we performed a new high-quality CCSD(T)/complete-basis-set study of the potential energy curves of 6 H-bonded complexes. Postdoc Lori Burns did a phenomenal job shepherding through the thousands of individual energy computations that were required to complete these projects. She also wrote extremely helpful Perl scripts to automate the collection and analysis of the data. These scripts will be helpful in our future work as well.

In the course of our testing of DFT-D/double-hybrid methods for noncovalent interactions, we realized that some of these methods are accurate enough that futher benchmarking and evaluation is hampered by the lack of very-high-quality benchmark data. We therefore re-evaluted the energies of the popular S22 test set of van der Waals dimers, and our new data should be accurate within a few hundredths of one kcal $\text{mol}^{-1}$. This was published in JCP, 2010.

In additional related work, we collaborated with Erin Johnson, Axel Becke, and Gino DiLabio to investigate the sensitivity to integration grid of several popular density functional methods in the context of non-covalent interactions. Meta-hybrid generalized gradient approximation functionals are found to be particularly sensitive to gridsize [JCP 2009].

We tested the performance of several popular molecular-mechanics methods for nonbonded interactions by benchmarking against our very high quality quantum mechanical potential curves for small model systems [J Comput Chem 2009]. This work inspired us to begin developing our own polarizable force field, and very impressive work by a summer student supported on this grant, Jarrod McClean, provided

us with a new and highly-accurate method. We parameterized this method using our latest benchmark quantum data for noncovalent interactions, and we are now beginning to test its effectiveness.

In related work, in collaboration with Kenneth Merz, we examined the accuracy of molecular mechanics estimations for nonbonded contacts that appear in drug binding; in particular, we examined the complex of indinavir with HIV-II protease. This resulted in one publication so far [JCTC 2010].

We have also embarked upon more speculative projects in collaboration with Prof. Alex Gray (Georgia Tech College of Computing). We are attempting to find out if general, tree-based $N$-body algorithms developed by Gray's group can be useful in chemistry. Initially, we have focused on two areas: (1) the very efficient computation of three-body triple-dipole dispersion terms (Axilrod-Teller-Muto) in molecular dynamics simulations of rare gas atoms, and (2) improved tree-based approaches for Hartree-Fock computations that may outperform fast multipole methods. We completed the implementation of this method in early 2009, and we are now in the process of testing the code and performing preliminary simulations. Although we had an opportunity to allocate resources to this work in 2007-2008, these resources had to be reallocated to maintain work on our primary objectives in 2008 and beyond. Fortunately, an NSF grant to our collaborator based on this work allowed it to continue, and we hope to report unprecedented three-body simulations of liquid argon in the near future.

In collaboration with Prof. Anna Krylov (USC), we have used our group's highly developed full configuration interaction program to benchmark the performance of equation-of-motion ionization-potential (EOM-IP) coupled cluster methods for radical cation dimers. These are very important in organic electronics.

We have also developed our own notes on configuration interaction gradients as a prelude to adding this capability to PSI3. Although CI gradients were fully developed in the 1980's, changes in notation and progress ways of formulating the problem mean that the older papers are not necessarily the best place to look for optimal, programmable equations. We believe that analytic frozen-core CI gradients may be a useful addition to PSI3 in cases of large nondynamical correlation (exactly the kind of situation we have examined often in the past). Our notes have been made publicly available on the Web, along with our extensive collection of other notes on quantum chemistry. Student Ed Hohenstein implemented RHF CI gradients based on these notes, and the resulting code gives correct results as checked by gradients computed numerically from energy points.

In collaboration with the Schaefer group at UGA, we have implemented a more efficient version of our MP2-CCSD hybrid theory, which aims to achieve good CCSD quality at a lower MP2-type cost. Additional tests of this approach are being run using the new code.

Finally, in preparation for the next grant period, we laid the foundation for a new effort in symmetry-adapted perturbation theory (SAPT). Using density fitting technology added to PSI in 2009, we implemented what we believe is currently the world's fastest SAPT program. This resulted in two publications in JCP in 2010. We will continue to extend and develop the theory and program through the completion of this grant and into the new grant period as discussed in the renewal proposal.

## Chemical Applications

We have published a careful theoretical study of hydrogen transfer reactions which examines the role of basis set and correlation effects and the comparison of computed barrier heights to experimentally inferred activation energies. Comparison to full configuration interaction results for some smaller systems was particularly unique and noteworthy.

Our publications on benchmark-quality potentials for non-covalent interactions have been very successful and have influenced the research of a significant number of computational chemists and theorists worldwide. Recently, we have sought to reach beyond these successful studies to ask much broader questions, such as: *How do non-covalent interactions afffect biomolecular structure? How do they influence lattice energies of aromatic, organic solids?* We published one paper in *Protein Science* which finds a remarkable correspondence between potential energy minima of the simple model complex $H_2S$-benzene and the geometrical preferences actually observed in cysteine-aromatic contacts in the Protein Data Bank. We published another paper in *Chem. Eur. J* which provides the first *ab initio* theoretical determination of the lattice energy of an organic solid (namely, crystalline benzene) to within "chemical accuracy" (1 kcal $mol^{-1}$). We also published a very detailed article examining substituent effects in parallel-displaced $\pi$-$\pi$ interactions [PCCP 2008], and an article showing the cumulative effect of dispersion interactions in multiply-substituted benzene dimers [JACS 2009]; another paper examined how heteroatoms effect $\pi$-$\pi$ interactions [JPC A 2009]. With undergraduate student Yue Geng, we performed the first benchmark-quality study of indole-benzene, giving insight into $\pi$-$\pi$ interactions between aromatic side-chains in proteins. These results are also helpful for extending the foundational principles of rational drug design.

We have also examined the importance of higher-level electron correlation in excited electronic states of the isocyanogen molecule (CNCN) at the behest of Prof. Robert Field at MIT, who requested assistance in assigning spectra of this molecule.

# Project Findings

## Theory development

We provided the first systematic study of Grimme's spin-component-scaled second-order many-body perturbation theory (SCS-MP2) method for *potential energy curves* of noncovalent interactions [PCCP 2007]. We also examined, at the same time, the effect of density fitting and local correlation approximations. We find that the local approximation can be surprisingly bad when modest basis sets (aug-cc-pVDZ) are used; we believe we are the first to report this problem. However, the density fitting approximation is very good for noncovalent interactions. This has motivated much of our theoretical and programming work in 2009 and beyond. SCS-MP2 is an improvement over MP2 in almost all cases (except, e.g., methane dimer). The alternative parameters by Hill and Platts (SCSN-MP2) seem better than SCS-MP2 in several instances, but not always. Subsequent work in our group on parallel-displaced benzene dimers suggests that SCS-MP2 may be more reliable overall.

We were the first to introduce the spin-component-scaled coupled-cluster singles and doubles (SCS-CCSD) method, which provides marked improvement over SCS-MP2 for reaction energies and noncovalent interactions [JCP 2008]. As Grimme has pointed out in a private communication, our demonstration that SCS-CCSD works just as well for methane dimer as for other cases is very notable (this is not true for SCS-MP2). Pavel Hobza highlighted the excellent performance of our SCS-CCSD approach in his plenary lecture at the Molecular Quantum Mechanics 2010 conference in Berkeley, and he subsequently re-optimized the scaling parameters specifically for noncovalent interactions to yield a SCS-CCSD method tuned for molecular interactions, SCS(MI)-CCSD.

We found that, overall, equation-of-motion ionization-potential coupled-cluster singles and doubles (EOM-IP CCSD) is rather reliable for radical cation dimers, which are of interest to organic electronics applications as well as small-molecule spectroscopy but which are very challenging theoretically because of symmetry breaking issues. The EOM CC results were benchmarked against full configuration interaction results from our group's highly-optimized full CI program, DETCI. This work was published in JCP (2007).

To aid our own work and assist other researchers in testing new methods for noncovalent interactions, we improved the quality of benchmark energies for the S22 test set of van der Waals dimers [JCP 2010], revising the interaction energies by as much as 0.6 kcal $\text{mol}^{-1}$ in some cases. The new benchmarks should have an accuracy of a few hundredths of one kcal $\text{mol}^{-1}$. This work has already garnered about 10 citations in its first year since publication.

We discovered that DFT-D does well compared to our benchmark-quality results for noncovalent interactions, and it outperforms M05-2X for long-range dispersion interactions (intermolecular distances beyond about 5 Å); this is important in interstrand base pair interactions in DNA [JCTC 2008]. We found that molecular mechanics force fields are qualitatively but not quantitatively correct for non-covalent $\pi$-

$\pi$ interactions. We found that meta generalized-gradient-approximation DFT methods exhibit serious numerical errors unless large integration grids are used, and we published a paper on the origins of this problem in collaboration with Becke, Johnson, and DiLabio (2009). Using our DFT-D code, we assisted Georgia Tech Professor Facundo Fernandez in interpreting experimental results for the rapid screening of the drug tamiflu, which will help in efforts to arrest drug counterfeiting in the third world.

Finally, we introduced density fitting into wavefunction-based symmetry-adapted perturbation theory (SAPT). This allowed us to develop the world's fastest SAPT program. SAPT0 and SAPT2 levels (including zeroth-order or second-order, respectively, intramonomer correlation effects) were implemented and published [two papers in JCP, 2010]. Even more efficient factorizations, additional approximations, and higher-order terms are being developed in the renewal period.

## Chemical applications

We have published two papers to date on hydrogen transfer reactions in simple organics or systems containing at most one other Group(IV)-A element. Our papers carefully elucidate basis set and electron correlation effects. Barrier heights can be somewhat sensitive to basis sets beyond cc-pVDZ, but electron correlation effects are adequately captured for these systems by CCSD(T) (as judged by comparison to full CI results, a notable feature of this work). We found and elucidated the difficulties in comparing computed barrier heights to activation energies deduced by experiment.

In work on noncovalent interactions, we have come to the remarkable conclusion that high-accuacy quantum results for very small model systems can have significant implications even for biomolecular structure or for crystal lattice energies. Amazingly, the geometric preferences exhibited by the simple $H_2S$-benzene model are actually observed in contacts between free cysteines and aromatic side-chains in histograms of S-$\pi$ contacts derived from the Protein Data Bank (PDB). This suggests that secondary interactions, solvent effects, etc., do not wash out (statistically) the fundamental preferences observed for the isolated noncovalent interactions.

In our work on crystalline benzene [*Chem. Eur. J*, 2008] we were the first to publish *ab initio* predictions of the lattice energy of an organic crystal to within chemical accuracy. This work demonstrates a theoretical protocol capable of achieving this accuracy. We believe this will be a landmark paper in the theoretical prediction of lattice energies and, by extension, have significant influence on theoretical determinations of crystal structures.

In the first systematic study of substituent effects in parallel-displaced $\pi$-$\pi$ interactions, we found that direct substituent-$\pi$ interactions are critical for understanding the potential energy surface [PCCP, 2008]. We also found that the effect of the substituent can vary across the potential energy surface, enhancing the interaction at some geometries, and decreasing it at others. We found that relatively small differential dispersion effects due to substituents in benzene dimers can become much larger for multiply-substituted benzene dimers, such that electrostatic-only models give large errors [JACS 2009]. This work has gen-

erated significant interest among experimental chemists working on molecular recognition, and in the future we aim to collaborate with Ken Shimizu (U. South Carolina) to help connect theory and experiment in quantifying the role of differential dispersion effects in $\pi$-$\pi$ interactions. We published benchmark-quality studies of indole-benzene [JPC A 2010] to shed light on the fundamental forces of $\pi$-$\pi$ interactions between side-chains in proteins.

We found that triple excitations (included via the CC3 model) can be quite important in predictions of the electronic spectrum and properties of excited electronic states for isocyanogen (CNCN). We believe our final results for the ground and low-lying singlet states will help explain recent spectra taken by the Field group at MIT.

We found that cation-$\pi$ interactions can be significant for off-axis configurations, and in the gas phase they remain attractive even if the cation is in the same plane as the ring. This counterintuitive result may be of relevance in explaining biomolecular structure [JPC A 2009].